

VolREthics Initiative - Volunteers in Research and Ethics

North America Workshop, October 19, 2022

“Focus on the risks of exploitation of healthy volunteers in biomedical research in North America”

Meeting report

Meeting agenda:

→ ***The VolREthics Initiative - Learnings from the first plenary meeting (10:00 – 10:10 am)***

François Bompard (Drugs for Neglected Disease initiative & Inserm Ethics Committee)

→ ***Overview of the HealthyVOICES and CMORE projects (10:10 – 10:20 am)***

Jill A. Fisher & Rebecca L. Walker (University of North Carolina at Chapel Hill)

→ ***Exploitation in North American Healthy Volunteer Research: Ethical and Practical Considerations (10:20 – 10:50)***

Trudo Lemmens (University of Toronto, Canada)

Seema Shah (Northwestern University, USA)

Roberto Abadie (University of Nebraska, USA)

→ ***Experiences of North American Healthy Volunteers: Phase I Drug Trials (10:50 – 11:20)***

→ ***Open discussion with the audience: identified risks of exploitation, field experiences, recommendations (11:20 – 11:50)***

→ ***Concluding Remarks (11:50 – 12:00)***

Jill A. Fisher & Rebecca L. Walker (University of North Carolina at Chapel Hill)

François Hirsch (Inserm Ethics Committee)

Attendees: a total of 80 persons registered to attend the meeting, primarily from the USA and Canada but also from Cameroon, China, France, Germany, Ghana, Japan, Liberia, Malaysia, Nigeria and Tanzania, including 4 US healthy volunteers.

Introductory presentations were made

1. The University of North Carolina's "HealthyVOICES" and "CMORE" projects were briefly described. These projects involved 180 healthy volunteers and 100 other key informants respectively. The UNC team has described *"a research context that differs markedly from most other clinical research, including by enrolling disproportionate numbers of economically disadvantaged people of color as participants. Due to these unique trial features and participation patterns, traditional biomedical research oversight offers inadequate ethical and policy guidance for phase I healthy volunteer research."* Based on these experiences, a recent paper was published that details five ethical criteria crafted to be responsive to the particularities of this type of research:
 - translational science value
 - fair opportunity and burden sharing
 - fair compensation for service
 - experiential welfare, and
 - enhanced voice and recourse.

Reference: Walker, R. L., D. MacKay, M. Waltz, A. D. Lyerly, and J. A. Fisher, "Ethical Criteria for Improved Human Subject Protections in Phase I Healthy Volunteer Trials," *Ethics & Human Research* 44, no. 5 (2022): 2-21. DOI: 10.1002/eahr.500139

<https://onlinelibrary.wiley.com/doi/full/10.1002/eahr.500139>

2. A presentation on the notions of coercion and undue influence/undue inducement was made.

Post-meeting note: The speaker alluded to Canada's TCPS2 (2018) guidelines that make specific reference to healthy volunteers involved in Phase I studies. This is worth highlighting since healthy volunteers are very rarely, if ever, considered as a specific population of human subjects participating in research deserving specific consideration in international and national guidelines:

Phase I

Safety concerns are particularly acute in phase I research because it may be the first time participants are exposed to the new drug ("first-in-human" trials), and there may be little or no experience with the drug. Phase I trials often depend on healthy participants who are offered incentives for their participation, or they may include participants with specific diseases for whom conventional therapy has failed. The combination of clinical risk with uncertain or no likelihood of clinical benefit, and the often substantial incentives offered to participants, raises ethical concerns about safety, the selection and recruitment of participants, and the consent process. For safety, it is important to ensure that the drug is initially given to a small number of participants and that dosing is increased in clearly defined increments only after participants' responses to the initial dose is known. Recruitment and consent procedures shall ensure that participants are aware of the untested nature of the therapy and that participants do not accept, because of the incentives being offered, risks they would otherwise refuse. Consideration should be given to minimizing the possibility of therapeutic misconception.

Source: https://ethics.gc.ca/eng/tcps2-eptc2_2018_chapter11-chapitre11.html

3. A presentation discussed the specific case of Controlled Human Infection studies. The profile of CHI volunteers seems somewhat different from that described by the UNC team, with more diverse levels of economic vulnerability, a lesser proportion of people of color, and more mixed motivations for participation that include altruistic and sometimes “experiential” motivations (e.g. get a personal malaria attack experience). The presenter proposed that one way to address the risk of exploitation is to decrease the level of risk to which volunteers are exposed but also to increase the level of financial benefits for healthy volunteers. The presenter acknowledged that this approach to financial compensation may be seen as more acceptable in the US and the UK than in other countries. She also referred to a situation where volunteers participating in a Zika study in Brazil expressed discontent at not having been informed of the outcomes of the study they took part in.
4. A researcher shared his experience of being immersed for 18 months in a group of healthy volunteers in the Philadelphia area who routinely took part in 8-10 studies a year. The volunteers described themselves as “professional guinea pigs” who experience dehumanization when considered just as bodies. They also saw themselves as “workers” deserving a fairer share of the benefits of research. Exploitation was seen by most as an integral part of the capitalist system. The presenter advocated for better working conditions for healthy volunteers, higher pay, and limitation on the number of studies through a national registry.

During the meeting, 4 experienced healthy volunteers shared their insights on their involvement in biomedical research.

They highlighted a series of issues:

- Financial motivation is the paramount reason for considering participation in studies (“to pay the bills”). They felt underpaid for their services, while they help other people get rich. Volunteers feel they are not treated as persons or workers but as bodies.
- Participating in studies requires sacrifices: dedicated time for the study and for visits, having to travel, need to make provisions for children and pets’ care.
- Significant discomfort can be experienced (3 weeks lying in bed), return visits are a burden, and adverse events occur.
- Money is offered not only to attract but also to retain volunteers in a study through “completion bonuses,” given only if participants fully complete all required study components. Adverse events can be under-reported to benefit from the completion bonus at the end of the study. People feel they are punished if study staff withdraw them from the study due to adverse events.
- “Good” participants, especially repeat participants, that fully abide by the rules can be better treated by the study staff than the more “unruly” ones. Experienced volunteers know how to “behave well.” Being seen as a “good” participant results in preferential treatment, including having an advantage for being selected for future studies.
- Experienced volunteers know how to “clean” their body between studies by ingesting food and vitamin supplements in order to feel better and have better biological test results.
- There are recruitment tensions in specific geographic areas where many studies are performed. Some labs are reimbursing better travel expenses to attract volunteers from

other locations. Some investigators sometimes accept borderline lab data to avoid disqualifying a volunteer.

- There is a feeling that information on the study drugs is often hidden from volunteers by investigators and staff. The most experienced volunteers do their own research on the tested drugs before enrolling in a study. One very experienced volunteer has decided to participate only in studies involving FDA-approved drugs. Participants commented that the study staff may penalize healthy volunteers who choose not to participate in a study after they have consented, even though the reason they have changed their minds may be due to information in the consent form or the research they did on their own about the study drug.
- Although some healthy volunteers expressed interest in knowing results of particular studies (especially those where participants experienced specific negative effects), no participants had tried to learn final study results, and in general little interest was expressed for being informed of the final study results.
- Improvements are expected mostly in
 - o Respect for the participants
 - o The transparency on the drugs that are studied
 - o Lessening the amount of “completion bonuses” that are seen as disrespectful for participants, and instead improving overall pay.
 - o Travel costs reimbursement.

Insights were provided in the following areas

- The notion of exploitation is a complex one that is relevant for multiple aspects of life in an industrialised country.
- The idea of a national healthy volunteers’ registry to ensure the respect of “washout” periods and possibly limit the number of permitted studies was raised. During the discussion, it was said to have 2 sides: it may prevent excessive participation in studies, but also encroach on volunteers’ freedom to decide for themselves.
- There is a tension between the need to ensure freedom of volunteers to withdraw at any time without consequences and the need to fairly compensate volunteers who complete all the study requirements. One volunteer suggested reducing completion bonuses, and instead improving overall pay, as a way to better respect participants’ rights.

Please see below a list of useful links related with the presentations made during the webinar.

How to Protect Healthy Volunteers from Exploitation in Biomedical Research?

Webinar Resources

UNC Empirical Bioethics Projects on Healthy Volunteer Clinical Trials (PIs: Jill A. Fisher & Rebecca L. Walker)

HealthyVOICES Project website:

<https://healthyvoices.web.unc.edu>

CMORE Project website:

<https://cmore.web.unc.edu>

Key Publications:

- Walker RL et al. (2022) [Ethical Criteria for Improved Human Subject Protections in Phase I Healthy Volunteer Trials](#). *Ethics & Human Research*44 (5): 2-21.
- Fisher JA et al. (2021) [Phase I Trial Compensation: How Much Do Healthy Volunteers Actually Earn from Clinical Trial Enrollment?](#)*Clinical Trials* 18 (4): 477-487.
- Kalbaugh CA et al. (2021) [Healthy Volunteers in US Phase I Clinical Trials: Sociodemographic Characteristics and Participation Over Time](#). *PLoS ONE* 16 (9): e0256994.
- Walker RL, Cottingham MD, Fisher JA (2018) [Serial Participation and the Ethics of Phase 1 Healthy Volunteer Research](#). *Journal of Medicine and Philosophy* 43 (1): 83-114.
- Fisher JA et al. (2018) [Healthy Volunteers' Perceptions of the Benefits of their Participation in Phase I Clinical Trials](#). *Journal of Empirical Research on Human Research Ethics*13 (5): 494-510.
- Fisher JA et al. (2018) [Healthy Volunteers' Perceptions of Risk in U.S. Phase I Clinical Trials: A Mixed-Methods Study](#). *PLoS Medicine*15 (11): e1002698.
- See also: Fisher JA (2020) [Adverse Events: Race, Inequality, and the Testing of New Pharmaceuticals](#). New York University Press.

Exploitation of Healthy Volunteers (Trudo Lemmens, University of Toronto)

Key Publications:

- Lemmens T, Elliott C (2001) [Justice for the Professional Guinea Pig](#). *American Journal of Bioethics*, 1(2):51-3.
- Lemmens T, Elliott C (1999) [Guinea Pigs on the Payroll: The Ethics of Paying Research Subjects](#). *Accountability in Research*, 7(1):3-20.

- Lemmens T, Miller PB (2003) [The Human Subjects Trade: Ethical and Legal Issues Surrounding Recruitment Incentives](#). *Journal of Law, Medicine, and Ethics*, 31:398-418.

Ethics Projects on Controlled Human Infection studies (CHIs) (Seema K. Shah, Northwestern University)

Key Publications by Prof. Shah:

- Shah SK et al. [Ethics of controlled human infection to address COVID-19](#). *Science*. 2020 May 22;368(6493):832-4.
- Shah SK, Rid A. [Ethics of controlled human infection studies: past, present and future](#). *Bioethics*. 2020 Oct;34(8):745-8.
- Jamrozik E et al. [Key criteria for the ethical acceptability of COVID-19 human challenge studies: Report of a WHO Working Group](#). *Vaccine*. 2021 Jan 22;39(4):633-40.
- Kraft SA et al. [Exploring ethical concerns about human challenge studies: a qualitative study of controlled human malaria infection study participants' motivations and attitudes](#). *Journal of Empirical Research on Human Research Ethics*. 2019 Feb;14(1):49-60.
- Marsh A et al. Characterizing altruistic motivation in potential volunteers for SARS-CoV-2 challenge trials. *Forthcoming in PLoS One*.

Other References Included in Prof. Shah's Presentation:

- Miller FG, Grady C. (2001). [The ethical challenge of infection-inducing challenge experiments](#). *Clinical Infectious Diseases*, 33, 1028-1033.
- Bamberg B et al. (2016). [Ethical criteria for human challenge studies in infectious diseases](#). *Public Health Ethics*, 9, 92-103.
- Selgelid MJ, Jamrozik E. (2018) [Ethical challenges posed by human infection challenge studies in endemic settings](#). *Indian journal of medical ethics*, 3(4):263.
- Wertheimer A. (1999) *Exploitation*. Princeton: Princeton University Press.
- Stunkel L, Grady C. (2011) [More than the money: a review of the literature examining healthy volunteer motivations](#). *Contemporary clinical trials*, 32(3):342-52.
- Fisher JA et al. (2018) [Healthy Volunteers' Perceptions of the Benefits of their Participation in Phase I Clinical Trials](#). *Journal of Empirical Research on Human Research Ethics*, 13 (5), 494-510.
- Anomaly J, Savulescu J. (2019) [Compensation for cures: Why we should pay a premium for participation in 'challenge studies'](#). *Bioethics*, 7, 792-7.
- Roestenberg M, et al. (2018) [Experimental infection of human volunteers](#). *The Lancet Infectious Diseases*, 18 (10), e312-22.
- Lenharo M (2021) [What Do Researchers Owe Their Study Subjects? They let Zika scientists collect data from their kids. Then they heard nothing](#). *Slate*.
- Pike ER (2012) [Recovering from research: A no-fault proposal to compensate injured research participants](#). *American Journal of Law & Medicine*, 38(1):7-62.

- Lederer SE (2015) [Dying for Science: Historical Perspectives on Research Participants' Deaths](#). *AMA Journal of Ethics*, 17(12):1166-71.

Professional Guinea Pigs (Roberto Abadie, University of Nebraska)

Key Publications:

- Abadie R (2010) [The Professional Guinea Pig: Big Pharma and the Risky World of Human Subjects](#). Durham, NC: Duke University Press.
- Elliott C, Abadie R. (2008) [Exploiting a Research Underclass in Phase 1 Clinical Trials](#). *New England Journal of Medicine*, 358(22):2316-7.
- Abadie R (2011) Guinea Piging in Philadelphia *Anthropology Now* 3:3 (December 2011), pp 29-35. <http://digitalcommons.unl.edu/sociologyfacpub/597>
- Abadie R (2019) [The Exploitation of Professional "Guinea Pigs" in the Gig Economy: The Difficult Road From Consent to Justice](#). *American Journal of Bioethics*, 19 (9):37-9.